Variability in the stereoselective disposition of ibuprofen in patients with rheumatoid arthritis

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- 1 Patients suffering from rheumatoid arthritis received oral doses of 600 mg racemic ibuprofen ($n = 25$; RAC) or 400 mg (S)-ibuprofen ($n = 25$; S-IBU) in a double-blind, randomized parallel-group study.
- 2 The pharmacokinetic parameters of (S)-ibuprofen were not statistically different between treatments ($P > 0.05$). Comparing (S)- and (R)-ibuprofen within the group receiving the racemate significantly higher $C_{\max}$ (20.3 ± 5.3 vs 17.7 ± 4.4 $\mu\text{g ml}^{-1}$; $P < 0.02$; 95% confidence interval for differences (CI): 0.5–4.6), AUC (86.2 ± 23.5 vs 67.6 ± 26.6 $\mu\text{g ml}^{-1} \text{ h}$; $P < 0.001$; CI: 9.5–27.6), mean residence time (4.5 ± 1.1 vs 4.1 ± 1.2 h; $P < 0.01$; CI: 0.1–0.6) and renal clearance (0.8 ± 0.6 vs 0.0 ± 0.0 ml min^{-1} ; $P < 0.001$; CI: 0.5–1.0) values were observed for the (S)-enantiomer.
- 3 No difference was found ($P > 0.05$) between treatments in the percentage of the dose recovered in the urine as (R)- or (S)-ibuprofen plus metabolites (S-IBU: 80.2 ± 8.47 vs RAC: $74.1 \pm 14.0\%$).
- 4 Interindividual variation in the pharmacokinetics of (S)-ibuprofen following administration of the racemate was similar to that following the administration of the single isomer suggesting that chiral inversion is not a major factor contributing to variability in the disposition of this drug.

Keywords ibuprofen enantiomers pharmacokinetics variability rheumatoid arthritis

Introduction

Ibuprofen (2-(4-isobutyl-phenyl) propionic acid), a 2-arylpropionic acid, is a chiral non-steroidal anti-inflammatory and analgesic drug which is in clinical use as the racemate for the treatment of rheumatoid arthritis and a number of other painful conditions. The anti-inflammatory activity, as determined by *in vitro* inhibition of prostaglandin synthesis, resides almost exclusively in the (S)-enantiomer (Adams *et al.*, 1976). *In vivo* (R)-ibuprofen is inverted to the (S)-enantiomer (Caldwell *et al.*, 1988; Hutt & Caldwell, 1983) to the extent of 28 to 90% depending on the method of calculating the chiral inversion (Baillie *et al.*, 1989; Geisslinger *et al.*, 1990; Lee *et al.*, 1985; Rudy *et al.*, 1991, 1993). This corresponds to an interindividual variability in the range of dosage of active (S)-ibuprofen of 384 to 570 mg following administration of 600 mg of the racemate. It has been suggested that this inversion may contribute significantly to the variability in response to ibuprofen (Day & Brooks, 1987; Day *et al.*, 1988; Williams & Day, 1985). Furthermore, it is possible that this variability may be

even greater in patients than in healthy volunteers. Whether such variability might be reduced by administration of the single (S)-isomer is unknown.

Therefore, the present study was undertaken to compare variability in the disposition of (S)-ibuprofen following administration *per se* and in the form of racemic drug to patients with rheumatoid arthritis. The clinical evaluation of the two study formulations which was part of this investigation is reported elsewhere (Stock *et al.*, 1991).

Methods

Reference compounds

(R)- and (S)-ibuprofen were supplied by PAZ Arzneimittelentwicklungsgesellschaft mbH (Frankfurt/Main, Germany) with chemical and optical purities of

greater than 99%. Racemic ibuprofen (USP XXI/BP 80 quality) and its major metabolites (hydroxyibuprofen, carboxyibuprofen) were obtained from the Boots Company (Nottingham, United Kingdom). Racemic ibuprofen (lot S 6013) and (S)-ibuprofen (lot RA 13/1) were compressed to tablets of the same size containing 600 mg and 400 mg doses, respectively.

Patients

Fifty (35 female, 15 male) in-patients with classical rheumatoid arthritis (Steinbrocker II–III) were recruited. They had no previous history of allergy to aspirin-like drugs. Patients treated with diuretics, anticoagulants, antidiabetic agents, phenytoin, phenobarbitone or related compounds or corticosteroids were excluded from the study.

Study design

The study protocol was approved by the University of Erlangen Medical Ethics Review Committee, and patients took part after giving written informed consent. The study was conducted in accordance with the Declaration of Helsinki on biomedical research involving human subjects.

All NSAIDs were discontinued at least 3–7 days (according to half-life) before the start of the study. During this period patients were allowed paracetamol up to 4 g day⁻¹. Following enrollment in the study, patients were assigned in a random, double-blind fashion to one of two treatment groups matched for age, weight and creatinine clearance. The subjects had a mean (s.d.) age of 60 (12.5) and 56 (9.7) years, and a mean body weight of 67.4 (11.1) and 70.2 (19.8) kg in the racemate group and in the (S)-ibuprofen group, respectively. The mean (s.d.) creatinine clearances of the subjects were 115.1 (42.4) and 121.9 (46.7) ml min⁻¹ in the racemate group and in the (S)-ibuprofen group, respectively. To provide approximately equal doses of the active anti-inflammatory (S)-enantiomer one group ($n = 25$) received 400 mg (S)-ibuprofen and the other ($n = 25$) received 600 mg racemic ibuprofen. The drugs were given 1 h after a standard breakfast with 100 ml tap water. Pre-dose venous blood samples were taken for haematological and biochemical tests and assay of ibuprofen, followed by blood sampling into heparinized tubes at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, and 8.0 h after the dose. Urine was collected before drug intake and up to 24 h. Urine volume was measured and aliquots of urine and plasma were frozen immediately at -30°C with quality control samples pending analysis. For ethical reasons a second dose of ibuprofen was given 8 h after the first. On the following days (until day 14) the test drugs were given three times daily. The results of clinical assessments performed on the first day of treatment and weekly thereafter are reported elsewhere (Stock *et al.*, 1991).

Analysis of ibuprofen enantiomers and metabolites

(R)- and (S)-ibuprofen concentrations were measured by stereoselective h.p.l.c. assay and total drug and metabolites by achiral h.p.l.c., as described by Geisslinger

et al. (1989a). Ibuprofen enantiomers and its metabolites were assayed in urine samples before and after alkaline hydrolysis. The limit of quantification consistent with a precision of 10% or less was 0.1 $\mu\text{g ml}^{-1}$ for all analytes. The coefficient of variation over the calibration range of 0.1–50 $\mu\text{g ml}^{-1}$ of each enantiomer was less than 6%.

Data analysis

Non-compartmental pharmacokinetic analysis was carried out using the TOPFIT[®] software package (Heinzel, 1982). The terminal elimination rate constant (λ_z) was estimated by unweighted linear least-squares regression analysis of the linear segment of the log plasma drug concentration-time data. The terminal elimination half-life ($t_{1/2,z}$) was calculated from $0.693/\lambda_z$. Values of AUC were estimated using the linear and log-linear trapezoidal rules with extrapolation to infinity using $C_{\text{(last)}}/\lambda_z$. The extrapolated area was less than 11% of the total AUC. Plasma drug clearance (CL) was calculated by dividing the dose of enantiomer by its AUC assuming complete bioavailability. The renal clearance (CL_R) of unchanged drug was estimated from the total amount excreted in urine up to 8 h/AUC assuming complete excretion of unchanged ibuprofen within 8 h (Geisslinger *et al.*, 1989b). The mean residence time (MRT) was calculated from the area under the first moment curve (AUMC) divided by the AUC.

Statistical analysis

The mean and standard deviation (s.d.) were used to express the central tendency of the data. The pharmacokinetic parameters of the enantiomers were analysed using two-tailed Student's *t*-test for paired (within the racemate group) and unpaired (between groups) data. Chi-square statistics were used for categorical data. Differences between means were considered statistically significant if the *P* value was less than or equal to 0.05.

Results

Of the 50 patients enrolled into the study, one patient in each group could not be included in the pharmacokinetic analysis owing to blood sampling problems. Mean plasma concentrations of the ibuprofen enantiomers following administration of 400 mg (S)-ibuprofen or 600 mg racemate are shown in Figure 1. The pharmacokinetic parameters of (S)-ibuprofen were not significantly different for the two treatment groups (Table 1). Following administration of the racemate a significantly greater mean C_{max} for the (S)-enantiomer compared with that of the (R)-enantiomer was found (20.3 ± 5.3 vs 17.7 ± 4.4 $\mu\text{g ml}^{-1}$; $P < 0.02$; Table 1). In the racemate group the mean AUC and MRT values were also significantly greater for (S)-ibuprofen ($P < 0.001$, $P < 0.01$; Table 1). The mean elimination half-lives of (R)- and (S)-ibuprofen were not significantly different (Table 1). There was a 3.3-fold inter-individual variation in the $t_{1/2,z}$ of the (R)-enantiomer and a 3.0-fold variation in that of the (S)-enantiomer in the racemate group and a 2.6-fold variation in the (S)-ibuprofen group (Table

Table 1 Mean $\pm$ (s.d.) pharmacokinetic parameters describing the fate of the individual enantiomers of ibuprofen following oral administration of 400 mg of (S)-ibuprofen ($n = 24$) and 600 mg of the racemic drug ($n = 24$) to patients with rheumatoid arthritis (median values; ranges are given in parentheses)

	400 mg (S)-ibuprofen		600 mg racemic ibuprofen		
	(S)-IBU	Significance [†]	(S)-IBU	Significance [‡]	(R)-IBU
$t_{\max}$ (h)	2.3 $\pm$ 1.0 (2.3; 3.8)	NS	2.4 $\pm$ 0.7 (2.3; 3.0)	NS [-0.1–0.2] [§]	2.3 $\pm$ 0.9 (2.3; 3.3)
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	21.8 $\pm$ 6.0 (22.4; 19.9)	NS	20.3 $\pm$ 5.3 (19.5; 22.9)	$P < 0.02$ [0.5–4.6] [§]	17.7 $\pm$ 4.4 (17.4; 14.9)
AUC ($\mu\text{g ml}^{-1}\text{h}$)	77.3 $\pm$ 15.7 (75.2; 58.6)	NS	86.2 $\pm$ 23.5 (82.7; 98.8)	$P < 0.001$ [9.5–27.6] [§]	67.6 $\pm$ 26.6 (63.6; 103.7)
$t_{1/2,z}$ (h)	1.9 $\pm$ 0.6 (1.7; 2.2)	NS	2.1 $\pm$ 0.7 (1.9; 2.6)	NS [-0.2–0.3] [§]	2.0 $\pm$ 0.7 (1.8; 2.6)
MRT (h)	4.2 $\pm$ 1.3 (3.8; 5.1)	NS	4.5 $\pm$ 1.1 (3.9; 3.9)	$P < 0.01$ [0.1–0.6] [§]	4.1 $\pm$ 1.2 (3.6; 4.6)
CL (ml min^{-1})	90.3 $\pm$ 21.1 (89.0; 89.4)		—		84.4 $\pm$ 30.6 (78.7; 119.2)
CL _R (ml min^{-1})	0.8 $\pm$ 0.5* (0.7; 2.0)	NS	0.8 $\pm$ 0.6 (0.7; 2.4)	$P < 0.001$ [0.5–1.0] [§]	0.0 $\pm$ 0.0

[†]Comparison of parameters of (S)-ibuprofen between groups (Student's unpaired *t*-test).

[‡]Comparison of parameters of (S)- and (R)-ibuprofen within group (Student's paired *t*-test).

[§][95% confidence intervals for differences].

NS: not statistically significant.

* $n = 21$.

Figure 1 Mean ($\pm$ s.d.) venous plasma concentrations of (S)-ibuprofen (■) and (R)-ibuprofen (○) following administration of 600 mg racemic ibuprofen (a, $n = 24$) or 400 mg (S)-ibuprofen (b, $n = 24$) to patients suffering from rheumatoid arthritis.

2). The variation in plasma drug clearance was substantially greater for the (R)-enantiomer following racemate administration (4.3-fold) compared with that of the (S)-enantiomer following administration of (S)-ibuprofen (2.4-fold). Both (R)- and (S)-ibuprofen were cleared primarily by metabolism with renal clearance accounting for less than 1% of the total clearance (Table 1).

Total urinary recoveries up to 24 h were 74.1 and 80.2% for the racemate and the (S)-ibuprofen groups, respectively. After administration of (S)-ibuprofen (2×400 mg) significantly more (S)-ibuprofen (primarily as conjugates) was found in urine than following administration of 2×600 mg of the racemic drug (13.6 vs 10.2%, $P < 0.005$). About 20% of the dose was eliminated as hydroxylated metabolite and about 45% as carboxylated ibuprofen (Table 3).

Discussion

The AUC values of (S)-ibuprofen were not statistically different between the two treatment groups ($P > 0.05$) supporting our supposition that approximately equal doses of (S)-ibuprofen were provided by the two different formulations, namely 600 mg of the racemate and 400 mg of the single (S)-isomer. Furthermore, no statistically significant difference was found between both treatment groups with regard to efficacy and unwanted effects (Stock *et al.*, 1991).

Inter-individual variation in the kinetics of ibuprofen isomers in our patients was similar to that observed by others in healthy subjects irrespective of whether racemic drug or the single (S)-isomer was given (Table 2). As (S)-ibuprofen is not inverted this would suggest that chiral inversion of the (R)-isomer is not a major factor

Table 2 Inter-individual variation of pharmacokinetic parameters in patients suffering from rheumatoid arthritis calculated as max/min as compared with healthy subjects (data from literature)

	(S)-IBU (400 mg) (S)-IBU n = 24	(S)-IBU (300 mg) (S)-IBU n = 11*	Racemate (600 mg) (S)-IBU (R)-IBU n = 24 n = 24		Racemate (400 mg) (S)-IBU (R)-IBU n = 24 [§] n = 24 [§]		Racemate (600 mg) (S)-IBU (R)-IBU n = 11* n = 11*	
$t_{\max}$	16	6.5	4.0	5.3	2.7	2.7	8.0	7.5
$C_{\max}$	2.6	1.5	3.0	2.4	2.6	2.4	2.7	3.1
AUC	2.4	2.2	3.0	4.2	1.9	1.8	2.5	1.9
$t_{1/2,z}$	2.6	2.0	3.0	3.3	2.7	2.9	2.1	2.4
MRT	2.9	1.8	2.3	2.7	—	—	1.5	1.5
CL	2.4	2.2	—	4.3	—	1.7	—	1.9
CL _R	8.8	—	34	—	—	—	—	—

*Data from Geisslinger *et al.*, 1990.[§]Data from Avgerinos & Hutt, 1990.**Table 3** Mean $\pm$ s.d. cumulative renal excretion of ibuprofen enantiomers and metabolites up to 24 h after oral administration of 400 mg (S)-ibuprofen (twice daily, $n = 21$) and 600 mg racemic ibuprofen (twice daily, $n = 24$) expressed as a percentage of the daily dose

	800 mg (S)-ibuprofen Free (%)		1200 mg racemic ibuprofen Free (%)	
	Total [§] (%)		Total [§] (%)	
(R)-ibuprofen	—	—	0.0 $\pm$ 0.0	0.22 $\pm$ 0.33
(S)-ibuprofen	1.01 $\pm$ 0.56	13.6 $\pm$ 3.49*	0.71 $\pm$ 0.53	10.2 $\pm$ 4.11
Hydroxyibuprofen	5.74 $\pm$ 1.77	21.5 $\pm$ 3.15	6.08 $\pm$ 2.44	20.2 $\pm$ 4.11
Carboxyibuprofen	32.1 $\pm$ 7.58	45.1 $\pm$ 6.82	30.7 $\pm$ 9.12	43.3 $\pm$ 9.44
Total	38.9 $\pm$ 8.98	80.2 $\pm$ 8.47	37.7 $\pm$ 11.1	74.1 $\pm$ 14.0

* $P < 0.005$ (two sided t -test, unpaired), comparison between groups.[§]After alkaline hydrolysis.

contributing to variation in the disposition of (S)-ibuprofen after administration of the racemate. However, the clearance of (R)-ibuprofen exhibited a much greater range of variability than that of the (S)-enantiomer possibly reflecting variability in inversion (4.3 vs 2.4-fold, Table 2). Rudy *et al.* (1993) reported a relatively small variability in the fraction inverted from (R)- to (S)-ibuprofen (range 9–19% coefficient of variation) in patients with osteoarthritis despite considerable variation in the total clearance of ibuprofen (range 28–49% coefficient of variation). The same group used a stable isotope method to show that the inversion clearance of (R)-ibuprofen following racemate administration amounted to about half of its total clearance (Rudy *et al.*, 1991).

The time to reach peak plasma drug concentration ($t_{\max}$) exhibited considerable inter-individual variation in our investigation. This may be due to the fact that the drug was given after a standard breakfast (Geisslinger *et al.*, 1989b). Values of the calculated pharmacokinetic parameters were in the range of those reported previously for healthy subjects. There is disagreement in the literature as to the relative terminal elimination half-lives of ibuprofen enantiomers. Some studies reported

a parallel decline of the plasma concentrations of the enantiomers (Geisslinger *et al.*, 1990; Jamali *et al.*, 1988; Rudy *et al.*, 1991), whereas others observed a more rapid elimination of (R)-ibuprofen (Avgerinos & Hutt, 1990; Baillie *et al.*, 1989; Cox *et al.*, 1988; Lee *et al.*, 1985).

Total urinary recoveries over 24 h were in the range reported for healthy subjects (Baillie *et al.*, 1989; Evans *et al.*, 1989; Geisslinger *et al.*, 1989b; Lockwood *et al.*, 1983; Rudy *et al.*, 1991). The total renal recovery (% dose) of ibuprofen and metabolites was similar in the two treatment groups (80.2 vs 74.1%). In contrast, Rudy *et al.* (1991) noted a statistically significantly greater recovery in healthy subjects following (S)-ibuprofen as compared with racemate administration. Comparing the total renal excretion of (S)-ibuprofen (free and conjugated) between groups in our study a significantly higher recovery was observed in the group receiving the single (S)-isomer. This may be due to stereoselectivity in the glucuronidation of ibuprofen enantiomers as shown previously using a human hepatic microsomal preparation (ratio S/R $\sim$ 1.6; El Mouelhi *et al.*, 1987).

In conclusion, we have shown that disposition of ibuprofen isomers exhibits substantial interindividual

variation in patients with rheumatoid arthritis. Chiral inversion does not appear to be a major factor influencing variability in plasma concentrations of (S)-ibuprofen. Therefore, to the extent that pharmacokinetic variability might influence response to treatment, administration

of the single (S)-isomer may have no advantage over administration of the currently used racemate.

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